**Appendix Table 1**: Summary of T-helper Subsets Related to Apical Periodontitis and Periodontitis

| **T-helper Subsets*** | **General Characteristics and Functions** | **Molecular Features** | **Role in Chronic Oral Inflammation**** | **References***** |
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| Th1 | • Cell mediated inflammation<br>• Intracellular pathogen defense<br>• Delayed-type hypersensitivity reactions | • ***Major Associated Cytokines:*** IFN-γ, IL-2, IL-12 and TNF-α<br>• **Signature Transcription Factor(s):** T-bet, STAT4 | **Apical Periodontitis:**<br>• Disease progression and severity<br>• Associated marker (IFN-γ) observed in radicular cysts<br>**Periodontitis:**<br>• Disease progression and severity<br>• Elevated expression of IFN-γ and T-bet observed in human disease progression | (de Carvalho Fraga et al. 2013; de Vries et al. 2017; Dutzan et al. 2009; Fukada et al. 2009; Teixeira-Salum et al. 2010) |
| Th2 | • Multicellular parasite defense<br>• Allergic reactions (IgE-mediated hypersensitivity)<br>• Suppression of pro-inflammatory T cells (e.g. Th1, Th17) | • ***Major Associated Cytokines:*** IL-4, IL-5, IL-13, IL-9, IL-10.<br>• **Signature Transcription Factor(s):** GATA3, STAT6 | **Apical Periodontitis:**<br>• Associated cytokines observed in periapical granulomas<br>**Periodontitis:**<br>• Imbalance of Th1/Th2 associated with disease progression, autoreactive B cell development and osteoclast activity in chronic lesions<br>• Th2 infiltration negatively correlated to RANKL/OPG ratio | (Berglundh and Donati 2005; de Vries et al. 2017; Fukada et al. 2009) |
| Th17 (Homeostatic) | • Pathogen defense<br>• Mucosal barrier homeostasis and defense<br>• Cell mediated inflammation and autoimmune disease<br>• Phenotype Plasticity*: (e.g.* | • ***Major Associated Cytokines:*** IL-17A, IL-17F, IL-21, IL-22<br>• **Signature Transcription Factor(s):** RORγt, STAT3 | **Apical Periodontitis:**<br>• Disease progression and severity<br>• IL-17 expression associated with “active” lesions<br>• RORγt expression observed in periapical lesions<br>**Periodontitis:** | (Araujo-Pires et al. 2014; de Vries et al. 2017; Dutzan et al. 2018; Moutsopoulos et al. 2012; Tsukasaki et al. 2018) |

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| | *Th1, Treg, or Tfh-like conversion )* | | • Disease progression, severity and loss of immune tolerance<br>• Neutrophil recruitment and osteoclastogenesis<br>• Upregulation of IL-17 and RORγt observed in chronic lesions | |
| Th17 (Pathogenic) | • Pro-inflammatory (Th1-like) responses<br>• Association with autoimmune and chronic inflammatory disease | • ***Major Associated Cytokines:*** IL-17A, IL-17F, IL-21, IL-22, IFN-γ, GM-CSF<br>• **Signature Transcription Factor(s):** T-bet | **Apical Periodontitis:**<br>• *Not yet characterized*<br>**Periodontitis:**<br>• Disease progression and severity *(suggested)*<br>• Population expansion in disease progression reported | (Bunte and Beikler 2019; Dutzan and Abusleme 2019; Dutzan et al. 2018; Tsukasaki et al. 2018) |
| Treg | • Immune tolerance and homeostasis<br>• Regulate differentiation and activation of pro-inflammatory T cells (e.g Th1, Th17<br>• Phenotype Plasticity | • ***Major Associated Cytokines:*** IL-10, TGF-β<br>• **Signature Transcription Factor(s):** Foxp3, STAT5 | **Apical Periodontitis:**<br>• Stabilization of lesion expansion *(suggested)*<br>• Treg associated cytokines (IL-10, TGF-β, CCL4) observed concomitant with proinflammatory cytokines in periapical lesions<br>**Periodontitis:**<br>• Protective role *(suggested, controversial)*<br>• Enrichment of Tregs observed in disease progression<br>• Subset heterogeneity reported | (Alvarez et al. 2018; Cafferata et al. 2020; da Motta et al. 2020; Naufel et al. 2017; Rajendran et al. 2019; Samuel et al. 2019; Toledo et al. 2019; Wei et al. 2020) |
| Tfh (Follicular helper) | • T-cell dependent humoral immune | • ***Major Associated Cytokines:*** IL-21, IL-4, CXCL13 | **Apical Periodontitis:**<br>• *Not well characterized*<br>• Thf associated cytokines/marker | (Araujo-Pires et al. 2014) |

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| | responses (assist B cells)<br>• Isolated to secondary lymphoid organs<br>• Association with broad range of diseases; protective <u>or</u> pathogenic roles | • **Signature Transcription Factor(s):** Bcl-6 | expression reported in “active” apical granulomas<br>**Periodontitis:**<br>• *Not well characterized*<br>• Expansion of splenic Tfh populations associated with positive response to novel periodontitis vaccines in mice | |
| Th9 | • Pro-inflammatory responses (via IL-9)<br>• *Possible regulatory function (via IL-10)*<br>• Association with certain autoimmune and inflammatory diseases (e.g. asthma, SLE, IBD) | • ***Major Associated Cytokines:*** IL-9, IL-10<br>• **Signature Transcription Factor(s):** PU.1, IRF4 | **Apical Periodontitis:**<br>• Stabilization of lesion activity *(suggested)*<br>**Periodontitis:**<br>• *Not yet characterized* | (Aranha et al. 2013) |
| Th22 | • Immune tolerance and protection<br>• Stimulation of non-immune cells (e.g. osteoclasts, fibroblasts)<br>• Association with autoimmune disease (e.g. RA, SLE, MS, psoriasis); *Role and mechanism in pathogenesis not fully elucidated* | • ***Major Associated Cytokines:*** IL-22, IL-26, IL-33<br>• **Signature Transcription Factor(s):** AhR | **Apical Periodontitis:**<br>• Stabilization of lesion activity (*suggested)*<br>**Periodontitis:**<br>• Disease severity and osteoclast activity<br>• Increased IL-22 and AhR expression correlated to clinical attachment levels | (Aranha et al. 2013; Araujo-Pires et al. 2014; Diaz-Zuniga et al. 2017; Monasterio et al. 2019) |

AhR - Aryl hydrocarbon receptor; Bcl-6 - B-cell lymphoma 6 protein; IRF4 - Interferon regulatory factor 4; RORγt - Retinoic acid-orphan receptor;
T-bet - T box expressed in T cell*;* Summary of General characteristics and functions adapted from Raphael et al. (2015) and Crotty (2019)
**List does not fully represent all current known subsets*

***Mechanistic role of the various T-helper subsets is not fully understood in both periodontitis and apical periodontitis*
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**Appendix Table 2:** Th17 Cells Associated Systemic Autoimmune and Chronic Inflammatory Diseases

| **Immunologic and Chronic Inflammatory Diseases** | **Th17 Significance** | **Reference** |
|---|---|---|
| Multiple Sclerosis (MS) / Experimental Auto-immune encephalomyelitis (EAE) * | • Overexpression of IL-17A in CNS biopsies of MS patients<br>• Significant Th17 cell infiltration in active MS lesions<br>• Th17/Treg imbalance associated with MS pathogenesis<br>• Murine Models (EAE):<br>  ○ Associated with onset and severity of disease<br>  ○ IL-17A auto-vaccine prevents disease<br>  ○ Th17 cells accumulate in diseased CNS tissue | (Fletcher et al. 2009; Kebir et al. 2007; Langrish et al. 2005; Li et al. 2017; Lock et al. 2002; Ma et al. 2010; Matusevicius et al. 1999; Park et al. 2005; Tzartos et al. 2008; Uyttenhove and Van Snick 2006) |
| Type I Diabetes (T1D) | • Elevated serum IL-17 levels reported in T1D patients<br>• Th17 cells associated with progression of T1D<br>• IL-17 SNP associated with increased risk for T1D<br>• Murine Models:<br>  ○ Th17 cells indicated in pancreatic inflammation and correlated with insulitis (T1D model)<br>  ○ Th17 transfer model of T1D demonstrates onset and rate of disease progression akin to Th1 transfer—transferred Th17 cells transform to pathogenic phenotype (produce IL17 & IFNγ) | (Abdel-Moneim et al. 2018; Borilova Linhartova et al. 2016; Bradshaw et al. 2009; Espinoza et al. 2011; Kumar and Subramaniyam 2015; Li et al. 2014; Martin-Orozco et al. 2009; Reinert-Hartwall et al. 2015; Roohi et al. 2014) |
| Type II Diabetes (T2D) | • Increased IL-17 levels reported in serum of recently diagnosed T2D patients and correlated to TNF-alpha expression<br>• IL-17 implicated in induction mechanisms of insulin resistance and beta-cell apoptosis<br>• Murine Models:<br>  ○ Obesity associated with Th17 cell phenotype bias | (Abdel-Moneim et al. 2018; Butler et al. 2003; Chen et al. 2016; Hotamisligil 2006; Hotamisligil and Spiegelman 1994; Ip et al. 2016; Matthews et al. 1985; Ohshima et al. 2012; Zhang et al. 2014) |
| Rheumatoid Arthritis (RA) | • Th17 activity linked to onset and bone resorption disease phases through induction of TNF-alpha, IL-6, chemokines and osteoclastic mediators (i.e. metalloproteinases)<br>• Increased infiltration of Th17 cells in RA synovial fluid and elevated frequency of Th17 cells in peripheral blood associated with RA patients | (Chabaud et al. 1999; Doreau et al. 2009; Kim et al. 2013; Kirkham et al. 2006; Koenders et al. 2006; Koenders et al. 2005; Pene et al. 2008; Sasai et al. 1999; Sato et al. 2006; Shahrara et al. 2008; van |

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| | • Murine Models: (i.e. Collagen-induced Arthritis (CIA))<br>  ○ Disease attenuation/protection in IL-17 deficient, IL-1RA antagonist, and IL-17 neutralized antibody treatment mice | Hamburg and Tas 2018; Wang et al. 2012) |
| Inflammatory Bowel Disease (IBD) | • Genome-wide association studies significantly link IBD to Th17 pathways<br>• Th17 cells infiltrate and enrich in intestinal mucosa of IBD<br>• Commensal-specific T cells demonstrate bias towards pathogenic Th17 phenotypes<br>• Murine Models:<br>  ○ Th17 cells implicated in relationship between microbial dysbiosis and pathogenic, pro-inflammatory host response<br>  ○ Humanized mice with dysbiotic intestinal flora from human patients elicit bias towards colitogenic pathogenic Th17 populations<br>  ○ Th17 cells potently mediate colitis in transfer models via transformation to pathogenic Th17 phenotype and support of conventional Th17 cells | (Britton et al. 2019; Calderon-Gomez et al. 2016; Cao et al. 2015; Fujino et al. 2003; Harbour et al. 2015; Holtta et al. 2008; Huang et al. 2017; Jostins et al. 2012; Kobayashi et al. 2008; Nimmo et al. 2012; Pene et al. 2008; Ramesh et al. 2014; Rivas et al. 2011; Schirmer et al. 2019; Ueno et al. 2018; Wilson et al. 2007) |
| Systemic Lupus Erythematosus (SLE) | • Th17 responses correlated to SLE disease activity<br>• Th1/Th17 imbalance and IL-6 dysregulation indicated in pathogenesis<br>• Elevated IL-17 and IFN-γ levels in peripheral blood mononuclear cells (PBMCs) and T-cells from draining lymph nodes in patients with SLE<br>• IL-17 promotes survival and proliferation of human B-cells<br>• Elevated IL-17 cytokine levels in patients with SLE-associated nephritis<br>• Murine Models:<br>  ○ Lupus-prone MRL/lpr mice demonstrate elevated expression of IL-17<br>  ○ IL-13 receptor deficient mice are protected from lupus nephritis in lupus-prone mice and demonstrated reductions in Th17 cells in lymph nodes | (Doreau et al. 2009; Jacob et al. 2009; Kwan et al. 2009; Kyttaris et al. 2010; Shah et al. 2010; Wang et al. 2010; Yang et al. 2009; Zhang et al. 2009; Zhao et al. 2010) |
| Sjogren's Syndrome (SS) | • Infiltration of Th17 cells and presence of IL-17 in glandular tissues of primary Sjogren's syndrome (pSS)<br>• Increase in circulating Th17 cells in pSS patients | (Iizuka et al. 2015; Lin et al. 2015; Lin et al. 2011; Verstappen et al. 2018; Verstappen et al. 2017; Voigt et al. |

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| | • Role of pathogenic plasticity suggested in disease activity and progression<br>• Murine models:<br>  ○ Th17 cells drive disease<br>  ○ IL-17 promotes autoreactive B-cell responses | 2016; Wanchoo et al. 2017; You et al. 2015) |

*EAE is an animal model of multiple sclerosis/central nervous system inflammatory demyelinating disease
Examples and descriptions of Th17 involvement in autoimmune and chronic inflammatory diseases included. These diseases have been shown to clinically associate with periodontitis and/or apical periodontitis. Notable corresponding references listed. *Note: Table provides limited summary of Th17 associated diseases and roles. For comprehensive reviews see (Kamali et al. 2019; Korn et al. 2009; Maddur et al. 2012; Weaver et al. 2007; Yasuda et al. 2019).*

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